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EXAMINER	
STRZELECKA, TERESA E	
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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *152-170* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *152-170* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed January 17, 2008. Claims 152-170 were previously pending. Applicants did not amend any claims.

2. Applicants' arguments did not overcome any of the previously presented rejections for reasons given in the "Response to Arguments" section below.

Response to Arguments

3. Applicant's arguments filed January 17, 2008 have been fully considered but they are not persuasive.

Regarding the rejection of claims 152-170 under 35 U.S.C. 103(a) over Goodey et al., Dromard et al., Fisher et al., Ohmura et al. and Tayot et al., Applicants argue the following:

A) There is no motivation to combine Goodey et al. and Dromard et al., since Dromard et al. teach purification of albumin from plasma, while Goodey et al. teach purification of recombinant albumin, since the impurities in the preparation of recombinant albumin are different from the ones in plasma. Applicants further argue that the combination of Goodey et al. and Dromard et al. fails to disclose or suggest an albumin concentration for negative mode CE of 10-250 g/L or that using such concentration would have been successful, since the levels of purification obtained by Dromard et al. decreased with increasing loading concentration. Finally, Applicants argue that they found that using high loading concentrations resulted in unexpected results of the impurities being more efficiently removed, as provided by the declaration of Stephen Berezenko filed May 15, 2006.

B) Regarding the combination of Goodey et al. and Fisher et al., Applicants argue that a rejection over Goodey et al. and Fisher et al. was withdrawn earlier in prosecution.

C) Regarding the combination of Goodey et al. and Tayot et al., Applicants argue that there would be no motivation to combine Goodey et al. and Tayot et al., since Tayot et al. teach

purification of albimun from serum, not a recombinant albumin, and Tayot et al. do not teach or suggest loading concentrations of 10-250 g/L.

D) Regarding the combination of Goodey et al. and Ohmura et al., Applicants argue that Ohmura et al. do not teach CE run in negative mode with respect to albumin or a loading concentration of 10-250 g/L.

First, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants dissected the rejection into different pairs of references with Goodey et al. However, the rejection provides the references of Dromard et al., Fisher et al., Ohmura et al. and Tayot et al. to establish the fact that both recombinant and plasma albumin can be purified using anion exchange chromatography run in the negative mode with respect to albumin incorporated into different purification protocols, and provide advantageous results with respect to protein structural integrity and purity level. In terms of the loading concentration, Goodey et al. provides evidence that the loading concentration can be adjusted according to the protocol, therefore one of ordinary skill in the art would not have a problem adjusting loading concentration of albumin. Further, Applicants' arguments that Dromard et al. teach away from using higher loading concentrations because they show increased impurities with increased loading concentration is not persuasive, as Applicants do not claim any particular levels of impurities in the final product. Finally, as to the unexpected results presented in the declaration of Dr. Philip Morton (not Stephen Berezenko), they were found to be not persuasive in an office action dated August 8, 2006. Applicants claim the range of 10-250 g/L of albumin concentrations loaded onto the CE column, but the declaration provides only four concentrations: 5,

25, 50 and 100 g/L, which is not commensurate with the scope of the claims. As can be seen in the presented table, at the highest albumin concentration of 100 g/L, the contaminant level has actually increased from the 50 g/L sample. As no other albumin loading concentrations were presented, it is not clear if the trend of increasing contaminant level continues with an increase of albumin loading concentration. Therefore, Applicants showed that the decrease in contaminant level was achieved for loading albumin concentrations from 5 to 50 g/L, which does not provide support for the claimed range.

Therefore, faced with the teachings of all of the cited references one of ordinary skill in the art would be motivated to add another purification step to the method of Goodey et al. to improve the efficiency of removal of impurities.

The rejection is maintained.

Claim Interpretation

4. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted.

A) "Chromatography in the negative mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix.

B) The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

C) A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C).

MPEP 2144.04 IV

C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 152-170 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action), Dromard et al. (U.S. Patent No. 4,675,384), Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in a previous office action), Ohmura et al. (EP 0570916 A2; cited in the IDS) and Tayot et al. (Develop. Biol. Standard., vol. 67, pp. 15-24, 1987; cited in the IDS).

A) Regarding claim 152, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).); and

wherein the albumin solution subjected to the cation exchange chromatography step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250g.L^{-1} (Goodey et al. teach adjusting the concentration of albumin between different purification steps to within the specified range (page 21, line 8; page 23, line 25; page 24, line 23; page 32, lines 10 and 25; page 33, line 21; page 37, line 10; page 39, line 9).

Regarding claims 154 and 155, Goodey et al. teach adjusting albumin concentration between different purification steps to within the specified range (page 21, line 8; page 23, line 25; page 24, line 23; page 32, lines 10 and 25; page 33, line 21; page 37, line 10; page 39, line 9).

Regarding claims 156, 158, and 159, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claim 157, Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation

chromatography before AE chromatography (page 2, lines 6-31; page 3, lines 1-16).

Regarding claims 160 and 161, Goodey et al. teach initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 164 and 168, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claim 165, Goodey et al. teach the pH of albumin solution applied to anion exchange column of 4.5-6.0 (page 25, line18).

Regarding claim 166, Goodey et al. teach fermentation before albumin purification (page 10, lines 12-31; page 11-15).

Regarding claim 167, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column

containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20);

(vii) subjecting the affinity chromatography eluate to an affinity chromatography step run in negative mode with respect to albumin and in positive mode with respect to glycoconjugates (Goodey et al. teach PBA column chromatography for binding glycoconjugates (page 36, lines 11-30; page 27, lines 1-18);

(viii) collecting the albumin-containing affinity chromatography flow-throgh (page 37, lines 8-21).

Regarding claim 170, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Regarding claims 152 and 167, Dromard et al. teach purification of albumin using steps involving anion exchange in positive mode with respect to albumin, followed by cation exchange step run in a negative mode with respect to albumin, followed by two or more ion exchange steps and affinity chromatography run in a negative mode with respect to albumin (col. 8, lines 46-68; col. 9, lines 1-13; col. 10, lines 50-68; col. 11, lines 1-55). This mode of purification produces albumin which has purity greater than 99% (col. 9, lines 26-31).

Regarding claim 153, Dromard et al. teach that albumin solution subjected to cation exchange step run in a negative mode with respect to albumin has a pH of 5.0 or higher (col. 8, lines 62-67).

Regarding claim 162 and 163, Dromard et al. teach that albumin solution subjected to anion exchange run in a negative mode with respect to albumin has a pH of 4.7 (col. 11, lines 32-42).

Regarding claims 152 and 167, Ohmura et al. teach purification of recombinant human serum albumin using cation exchange chromatography run in positive and anion exchange chromatography negative mode with respect to albumin (page 3, lines 1-9; page 6, lines 10-20; page 11, lines 11-50). The purification resulted in removal of yeast-derived proteins to undetectable levels (page 12, lines 16-28).

Regarding claims 152 and 167, Fisher et al. teach purification of albumin using cation exchange and anion exchange steps run in a negative mode with respect to albumin and teach that order of the two steps is not critical (col. 2, lines 22-40; col. 3, lines 29-68; col. 4, lines 1-22).

Finally, Tayot et al. teach a large-scale preparation of albumin using cation exchange exchange chromatography step run in a negative mode with respect to albumin (page 19, i-vii; page 20).

Tayot et al. teach initial albumin concentration of 31 g/L (page 20, first paragraph).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the ion exchange chromatography steps run in a negative mode with respect to chromatin of Dromard et al., Ohmura et al., Fisher et al. and Tayot et al. in the method of albumin purification of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that such steps minimized potential alterations in the native structure of the albumin and reduction in handling or manipulation was advantageous in commercial applications

(col. 2, lines 4-10). The motivation to do so, provided by Tayot et al., would have been, as stated by Tayot et al. (page 19, iii):

"The low volume of the 3rd column (cation exchanger) is due to the deliberate choice of fixing the impurities selectively without fixing the albumin. It is more economical to fix the minority components than the main protein."

Thus, one of ordinary skill in the art faced with the teachings of Dromard et al., Ohmura et al., Fisher et al. and Tayot et al. would be motivated to alter the method of Goodey et al. to include steps run in a negative mode with respect to albumin which do not lead to protein structure alterations and protein losses.

7. No claims are allowed.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637

April 7, 2008